



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C12N 15/00, 15/12, C07K 14/00, 14/435</b>		<b>A1</b>	(11) International Publication Number: <b>WO 99/58660</b>
			(43) International Publication Date: 18 November 1999 (18.11.99)
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(22) International Filing Date: <b>6 May 1999 (06.05.99)</b>			
(30) Priority Data:			
60/085,093	12 May 1998 (12.05.98) US		
60/085,094	12 May 1998 (12.05.98) US		
60/085,105	12 May 1998 (12.05.98) US		
60/085,180	12 May 1998 (12.05.98) US		
60/085,927	18 May 1998 (18.05.98) US		
60/085,906	18 May 1998 (18.05.98) US		
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60/085,925	18 May 1998 (18.05.98) US		
60/085,928	18 May 1998 (18.05.98) US		
60/085,920	18 May 1998 (18.05.98) US		
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(54) Title: <b>97 HUMAN SECRETED PROTEINS</b>			
(57) Abstract			
<p>The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.</p>			

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1487 of SEQ ID NO:29, b is an integer of 15 to 1501, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 20

Preferred polypeptides of the invention comprise the following amino acid sequence:

GTPAGTGPEFPGRPTRPSRTESAQTTQHSPLRPLWRLKRDSSPCHPQTRADWG  
VCPWGGAAQGLRPGCH  
LAPRRCLCPGSCCPWHWAEAQWSFLWRGLWGLRTLPTALRASPAASGTVTY  
SACLGTSCLLRAPCWRLRT CRQSWC (SEQ ID NO: 275),  
GTPAGTGPEFPGRPTRPSRTESAQTTQH (SEQ ID NO: 276),  
SPLRPLWRLKRDSSPCHPQTRADWGVCPW (SEQ ID NO: 277),  
GGAAQGLRPGCHLAPRRCLCPGSCCPWHWA (SEQ ID NO: 278),  
EAQWSFLWRGLWGLRTLPTALRASPAASGT (SEQ ID NO: 279), and/or  
VTYSACLGTSCLLRAPCWRLRTCRQSWC (SEQ ID NO: 280). Polynucleotides encoding these polypeptides are also provided.

The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in osteoarthritis, breast cancer, and uterine cancer, and, to a lesser extent, in brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, cancer, particularly breast and uterine cancer; and neurological diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above

5 tissues or cells, particularly of the breast, lymph node, and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, breast, skeletal, joint, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an

10 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 130 as residues: Gln-75 to Cys-80.

15 The tissue distribution in breast and uterine cancer indicates that the protein product of this gene is useful for the diagnosis and/or treatment of a variety of cancers, particularly breast cancer and uterine cancer. Expression of this gene in brain also indicates that it may play a role in neurological function, and that its absence may lead to disorders such as Alzheimer's & Parkinson's disease. Expression of this gene

20 product at elevated levels within cancerous tissue indicates that it may be a player in the progression of the disease, perhaps by driving proliferation or blocking differentiation or apoptosis. Therefore, beneficial therapeutics may be developed based upon attempts to block this gene product.

Representative uses are described in the "Hyperproliferative Disorders" and

25 "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain

30 neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may

also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1738 of SEQ ID NO:30, b is an integer of 15 to 1752, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 21**

This gene shares sequence homology with a yeast hypothetical 52.9 KD protein CDC26-YMR31 intergenic region (See Genbank Accession No. gpID50617|YSCCHRVI\_114.). This gene has been mapped to chromosome 18q22-23, and therefore can be used in linkage analysis as a marker for 18q22-23.

30

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
12	HE2ES51	209745 04/07/98	Uni-ZAP XR	22	1447	1	1447	77	77	122	1	14	15	222
13	HTXDW56	209746 04/07/98	Uni-ZAP XR	23	1583	1	1583	217	217	123	1	22	23	201
14	HEEAG23	209745 04/07/98	Uni-ZAP XR	24	1669	25	1280	57	57	124	1	18	19	46
15	HDPKJ93	209745 04/07/98	pCMVSPORT 3.0	25	1053	1	1053	46	46	125	1	21	22	305
16	HDLAC10	209745 04/07/98	pCMVSPORT 2.0	26	1477	1	1477	132	132	126	1	29	30	81
17	HDPOH06	209745 04/07/98	pCMVSPORT 3.0	27	2504	1	2504	252	252	127	1	29	30	242
18	HCE4G61	209745 04/07/98	Uni-ZAP XR	28	1866	1	1866	130	130	128	1	23	24	285
18	HCE4G61	209745 04/07/98	Uni-ZAP XR	108	1779	1	1720	125	125	208	1	20	21	81
19	HCWUI13	209745 04/07/98	ZAP Express	29	1501	1	1501	80	80	129	1	18	19	157
20	HDPSP01	209745 04/07/98	pCMVSPORT 3.0	30	1752	1	1752	227	227	130	1	20	21	308
21	HHPEN62	209746 04/07/98	Uni-ZAP XR	31	2152	141	2152	183	183	131	1	27	28	508

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&lt;210&gt; 30

&lt;211&gt; 1752

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1099)

&lt;223&gt; n equals a,t,g, or c

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